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Influence of diet on chronic pain conditions

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Summary:

This review examines current knowledge about putative “pro-algesic” dietary components, and discusses whether limiting the intake of these substances can help improve chronic pain. Although there is a common impression that numerous food components, natural and synthetic, can cause or worsen pain symptoms, very few of these substances have been investigated. This article focuses on four substances, monosodium glutamate, aspartame, arachidonic acid, and caffeine, where research shows that overconsumption may induce or worsen pain. For each substance, the mechanism whereby it may act to induce pain is examined, and any clinical trials examining the effectiveness of reducing the intake of the substance discussed. While all four substances are associated with pain, decreased consumption of them does not consistently reduce pain.

Keywords:

arachidonic acid, aspartame, caffeine, diet, fibromyalgia, glutamate, headache, 6-omega polyunsaturated fats,

Expert commentary:

While an association between intake of certain dietary components and the exacerbation of pain conditions, such as headache, is not new, rigorous scientific investigation of these relationships is still limited. Food additives are, understandably,

subjected to a greater degree of investigation when they have been associated with the development of untoward effects such as pain. Early investigations were often commercially motivated and as a result tended to minimize any association between pain symptoms and the food additive. More recent examinations of food additives or dietary components with a suspected pain association identify monosodium glutamate (MSG) as having the strongest evidence for inducing or exacerbating existing pain, and aspartame as having the least. However, large, well designed clinical trials of dietary reduction of MSG to manage chronic pain conditions remain to be conducted, so the employment of this strategy to treat pain is not yet supported by evidence. On the other hand, as this type dietary modification has the potential to be pain reducing with few if any negative consequences, it will continue to be used by individuals who are looking for ways to treat their chronic pain. It is important that health care professionals who treat persons with pain can discuss this approach to pain treatment.

Five-year view:

The development, in 2012, of a new, state-of-the-art National Institutes of Health research program focusing upon the role of the brain in perceiving, modifying, and managing pain at the National Center for Complementary and Integrative Health, whose mission is to fund and conduct research on complementary health approaches, demonstrates the very high level of public interest in alternative approaches to treating chronic pain. The availability of increased funding in this area is likely to expand the

number of studies on the utility of dietary modification in the treatment of pain over the next 5 years.

Key issues:

1. Monosodium glutamate is found in many foods, resulting in an average consumption of 170-250 mg/kg/day.
2. Ingestion of a single dose of 150 mg/kg of MSG increases serum glutamate levels by up to 8 times normal and can result in reports of flushing, diffuse muscle aches, and headaches.
3. Daily ingestion of 150 mg/kg MSG leads to increased reports of headache and muscle tenderness in young, healthy men and women.
4. MSG sensitizes nociceptive nerve fibers and induces vasodilation of cranial blood vessels through activation of peripheral N-methyl-D-aspartate receptors.
5. Elevated glutamate levels have been found in temporomandibular disorders and migraine headache, and reduction of dietary glutamate intake may reduce muscle pain symptoms in fibromyalgia.
6. Daily consumption of aspartame is about 5 mg/kg, and at this level of intake, no association with pain conditions has been identified.
7. Increased consumption of arachidonic acid has not yet been linked to increased pain reports, but, in theory this could elevate prostaglandin and leukotriene levels to promote inflammatory pain.

8. Reduced intake of arachidonic acid and its precursor, linoleic acid, has been reported to reduce pain in rheumatoid arthritis and decrease the frequency of headaches in migraine.
9. Increased daily caffeine intake (> 400 mg/day) has been associated with the development of headaches.
10. Reduction of excessive caffeine intake has been shown to alleviate headache symptoms in some individuals, however, abrupt cessation of caffeine intake often causes headaches, which necessitates a slow taper of caffeine intake over 1-2 weeks.

Body of the Article:

Although strong associations have been made between the consumption of certain foods and chronic disease, notably cardiovascular disease, research that links diet to certain chronic pain conditions is still in its early stages. It is known that some foods can trigger pain or aggravate existing pain conditions. For example, consumption of gluten by individuals with gluten sensitivity can lead to gastrointestinal tract pain. Migraine headache is known to be triggered in some sufferers by specific foods like chocolate or wine [1-3]. However, less is known about the potential interaction between intake of specific dietary components and chronic pain conditions. Decreased intake of vitamins, for example B and D vitamin deficiencies, is associated with neuropathic pain conditions and muscle pain, respectively [4]. Likewise, overconsumption of certain dietary components or food additives, such as polyunsaturated fatty acids and aspartame, has long been speculated to contribute to or even cause pain under certain conditions. The concept that altered diet can be used to modify chronic diseases is also well accepted for conditions such as cardiovascular disease and diabetes. Whether diets that limit the intake of dietary components or food additives are effective in modifying chronic pain remains a subject of ongoing research. The aim of this review is to shed light on what is known about putative “pro-algesic” dietary components, and to discuss whether limiting the intake of these substances can help improve certain pain conditions.

Monosodium Glutamate (MSG) and Pain

MSG is a natural component of many foods, and is also added as a flavor enhancer. Ingestion of large quantities of MSG is theorized to have a negative effect on pain in chronic pain patients [5]. Glutamate-rich foods include condensed soup, Parmesan cheese and packaged sauces, particularly tomato sauce, and seasonings [6]. The median daily consumption of glutamate in the Western diet from all sources is around 12 g [7,8]. This is somewhere between 170 -250 mg/kg/day of glutamate. A single fast food meal of a hamburger and milk shake contains approximately this amount of glutamate and has been shown to elevate serum glutamate concentrations for about 6 hours, with peak concentrations reaching ~250% of baseline concentrations by 2 hours after consumption [9]. This suggests that diets high in glutamate could result in a sustained elevation of glutamate concentrations.

Association of MSG intake with pain.

Due to early reports of symptoms related to overconsumption of MSG, the acute effects of MSG administration have been fairly extensively examined. Single oral doses of 150 mg/kg in adults have been reported to increase serum levels of glutamate 30 minutes post ingestion by up to 800% [10]. A range of symptoms that include general weakness, muscle tightness, flushing/sweating, headache, paresthesias, arrhythmias and tachycardia have been reported after acute ingestion of MSG doses in this range [11-14]. Not all early studies conducted to investigate these MSG-induced effects consistently evoke these symptoms in healthy subjects, even if subjects reported they were “MSG sensitive” [7,14]. This led to suggestions that failure to adequately mask the

unique taste of MSG may have been responsible for the high incidence of adverse effects reported by some researchers [7,14]. However, the development of MSG-related symptoms has been found to be dose related, and oral administration of MSG results in highly variable serum glutamate concentrations [13], which may explain part of the variability in response to orally administered MSG. Indeed, intravenous administration of 5 mg/kg glutamate still results in reports of burning sensations, facial pressure or chest tightness in association with peak serum levels of glutamate [12]. Thus, the variability in symptoms reported after oral MSG ingestion most likely due to individual differences in the blood level of glutamate achieved after oral ingestion.

More recent studies support the concept that ingestion of large amounts of MSG can alter pain sensitivity in healthy, young men and women. In a double-blinded, placebo-controlled crossover study to investigate the effect of a single oral administration of 150 mg/kg MSG, a significant correlation between plasma glutamate level and muscle pain tolerance in the temporalis muscles was found [15]. There was also a significant increase in reports of headache and pericranial muscle tenderness after MSG [15]. Repeated administration of 150 mg/kg/day MSG for 5 days resulted in increased reports of headache and masseter muscle tenderness in healthy young adults [16]. Interestingly, peak interstitial glutamate concentrations in the masseter muscle and plasma were increased after repeated ingestion of MSG over 5 days (Figure 1) [17]. This result suggests that even short term increased intake of MSG results in tissue accumulation of glutamate, and that this may increase the risk of developing pain sensitivity.

Why does MSG Alter Pain Sensitivity?

How might ingestion of MSG lead to increased headaches and cranial muscle sensitivity? Previous research indicates that doses of up to 1g/kg of MSG do not cross the blood-brain barrier [18,19], which suggests that observed effects of systemically administered MSG are mediated by peripheral rather than central mechanisms. In rats, intravenously administered MSG (50 mg/kg) temporarily increases the interstitial concentration of glutamate in the masseter muscle from a baseline of 24 μM to a peak concentration of 63 μM [20]. This increase in glutamate concentration causes a decrease in the mechanical activation threshold and increase in the spontaneous action potential discharge of masseter muscle nociceptors [20]. The mechanical sensitization of masseter muscle nociceptors after intravenous MSG administration was attenuated by systemic administration of ketamine, a N-methyl-D-aspartate (NMDA) glutamate receptor subtype antagonist. Intramuscular injection of glutamate into the masseter muscle has also been shown to evoke brief (< 10 min) nociceptor discharges as well as induce a prolonged period (> 3 hours) of mechanical sensitization in cranial muscle nociceptors that are also mediated through activation of peripheral NMDA receptors [21-23]. Thus, the pain sensitizing effects of MSG appear to be mediated, in part, through activation of peripheral NMDA receptors expressed by a subgroup of masticatory muscle nociceptors [24-26].

Elevated glutamate concentrations also promote vasodilation of cerebral blood vessels. Glutamate-induced vasodilation is mediated through activation of NMDA receptors [21,27-30]. Glutamate-induced vasodilation appears to occur, in part, as a result of the release of the vasoactive neuropeptides calcitonin gene related peptide

(CGRP) and substance P, and the production of nitric oxide [27,29] . Thus, MSG-induced headaches probably occur as a result of the combination of cerebral vasodilation and nociceptor sensitization.

Can dietary restriction of MSG affect chronic pain conditions?

There is evidence that glutamate levels are elevated in migraine and tension type headache patients as well as in myofascial temporomandibular disorder patients. Multiple reports show that blood and salivary glutamate levels are elevated by 25-600% in migraine patients compared to healthy controls [31-35]. In addition, there is some evidence that glutamate levels in platelets are elevated in chronic tension-type headache sufferers [32]. Myofascial temporomandibular disorder (TMD) pain patients who report ongoing pain in their masseter muscle, have elevated interstitial concentrations of glutamate in this muscle compared to healthy controls [36]. These findings suggest that altered peripheral glutamate concentrations could be involved in the mechanism of generation of both migraine headache and myofascial pain.

Indirect evidence suggests that lowering blood glutamate concentration may be an important determinant of the effectiveness of migraine prophylactic therapy. It has been found that mean baseline fasting plasma glutamate in 24 episodic migraine headache without aura patients was ~60 μM as compared with ~ 10 μM in 24 age and sex-matched controls [35] . Patients fasting plasma glutamate levels were reassessed 8 weeks after initiation of a migraine prophylactic therapy (topiramate, propranolol, amitriptyline, or flunarizine). Effective migraine prophylaxis was associated with a drop

of glutamate from 60 μM to 20 μM . Nevertheless, even after effective prophylaxis treatment, migraine headache patients still had blood glutamate concentrations that were twice those of healthy controls. Whether a reduction in the consumption of MSG in migraine patients could also lead to decreased headache frequency has not been investigated.

The effectiveness of a reduction of dietary MSG intake and pain intensity has also been investigated in fibromyalgia patients, who suffer from chronic, widespread musculoskeletal pain. A case report suggested that 4 women with fibromyalgia had significant improvement in their muscle pain after decreasing MSG from their diets, although it is unclear from this report what their consumption of MSG was before and after the implementation of this “MSG-free” diet [37]. A more recent study of 72 fibromyalgia patients, which compared a restricted dietary intake of MSG and aspartame to no restriction in the diet, found no effect of reducing MSG intake on fibromyalgia pain [38]. However, it is unclear how effective the reduction of MSG intake was in this study, as data on MSG consumption at baseline and after the intervention were not reported. In another study, 57 fibromyalgia patients with irritable bowel syndrome were put on a 4 week diet that restricted intake of MSG (and aspartame), and then, responders to the diet were re-challenged with MSG or placebo in a double blind, crossover study [39]. It was reported that more than 80% of patients reported a 30% or better reduction in their pain on this diet. Twenty six of the responders, who remained on the low MSG diet, then received either placebo or MSG (5 g, ~60 mg/kg) containing juice, for 3 days each week, for a total 2 weeks. Visual analogue pain scores were 38% higher during the weeks when MSG was administered, compared

with the weeks when placebo was administered. The finding that pain in some fibromyalgia patients is affected by MSG consumption suggests that additional trials of low MSG diets are needed to determine whether this approach might be beneficial to treating pain and disability in this disorder.

Aspartame and Pain

Aspartame (l-aspartate-l-phenylalanine-methyl ester) is an artificial sweetener ~200 times sweeter than sugar [40]. It is estimated that daily aspartame intake in the US is about 5 mg/kg/day [40]. One of the most common complaints related to the ingestion of aspartame is the development of headache [41]. Aspartame is metabolized to aspartic acid, phenylalanine and methanol, with the aspartic acid usually considered the component most likely to potentially exacerbate pain [40].

Association of Aspartame with Pain

Placebo controlled studies in healthy volunteers have not found a greater incidence of headache after aspartame consumption (25-30 mg/kg/day) than placebo [42,43]. In a double-blind crossover study, which used volunteers with self-identified aspartame headaches, it was reported that headaches occurred only slightly more often on 30 mg/kg aspartame for 7 days than on placebo [44]. The stronger subjects associated aspartame with their headaches, the more likely they were to report an increased frequency of headache. However, in a small placebo controlled study in subjects who reported headache after ingestion of 150 mg/kg MSG but not placebo,

oral administration of 34 mg/kg aspartame did not provoke headaches or other symptoms [45]. Plasma aspartate concentrations did not significantly change after administration of this dose of aspartame [45].

Why Might Aspartame Alter Pain Sensitivity?

Aspartic acid is also a NMDA receptor agonist, and theoretically could act similarly to MSG, by activation of peripheral NMDA receptors. It is unclear what increase in interstitial aspartate concentration would be necessary to sensitize nociceptors in deep tissues.

Does dietary restriction of Aspartame alter chronic pain

A trial of dietary restriction of aspartame and glutamate in fibromyalgia patients found no significant effect on pain [38]. Given that the only pain condition aspartame is associated with is headache, it seems unlikely that restriction of aspartame intake alone would have any effect on chronic, widespread pain.

Arachidonic Acid and Pain

The move to reduce omega 3 fatty acids in commercially prepared foods has led to an increase in omega 6 polyunsaturated fatty acids in the modern diet [46].

Arachidonic acid is an n-6 (omega 6) polyunsaturated fatty that is consumed in animal based foods such as eggs and meat [47]. As humans are unable to synthesize

arachidonic acid de novo, it must either be consumed in the diet or synthesized from linoleic acid, an essential fatty acid, consumed in the diet [46,47]. As arachidonic acid is the precursor molecule for inflammatory and algogenic substances such as prostaglandins and leukotrienes, the effect of varying levels of this polyunsaturated fatty acid on pain is of significant interest.

Association of arachidonic acid with pain

Unlike glutamate and aspartame, increased consumption of arachidonic acid has not been associated with the development of pain conditions. It is not clear if there is a certain level of consumption of linoleic acid or arachidonic acid that would lead to complaints of increased pain, or what types of pain this might affect. It has been suggested that in certain neuropathic pain conditions like complex regional pain syndrome, patients appear to have an increased blood levels of metabolites of linoleic acid [47]. However, it is important to consider that linoleic acid is an essential dietary component, and if intake of this fatty acid is drastically reduced, effects on health, such as reproductive and immune dysfunction, occur [47]. Indeed, it is possible that certain pain conditions, such as diabetic neuropathy, could be made worse by reductions in the intake of linoleic or arachidonic acid, as diabetics have altered fatty acid metabolism.

Why could an increase in arachidonic acid intake alter pain sensitivity?

Cyclooxygenase and lipoxygenase act on arachidonic acid to produce prostaglandins and leukotrienes, respectively. Elevation of prostaglandin E2 and leukotriene B4 in tissues decreases mechanical and thermal nociceptive thresholds in

rats [48-50]. This could explain the association of elevated intake of arachidonic acid with altered pain sensitivity. Indeed, subcutaneous injection of high concentrations of arachidonic acid (≥ 10 mM) induces edema and lowers nociceptive thresholds in rats [51,52]. Linoleic acid does not alter pain sensitivity when injected acutely. However, it is not clear whether arachidonic acid has the same effect on pain if its intake is increased in the diet. In a model of rheumatoid arthritis, which was initiated by subcutaneous injection of complete Freund's adjuvant into the rat paw, rats fed an arachidonic acid rich diet had the expected elevated content of arachidonic acid in the paw skin [53]. However, there was no effect of this diet on arthritis-related increases in paw edema, or pathological joint changes such as bone erosion. Further, although arthritis induction significantly increased prostaglandin E₂, the concentration was not different in control animals and animals fed the elevated arachidonic acid containing diet. Since prostaglandin E₂ is one of the inflammatory mediators most associated with nociception, this suggests that the increased levels of arachidonic acid achievable by diet would not alter pain sensitivity, although additional research is needed to confirm this.

It has also been reported that 2-20 μ M arachidonic acid can potentiate NMDA receptor currents in cultured neurons [54-56]. This effect happens too rapidly to be explained by conversion of arachidonic acid to a prostaglandin or leukotriene and does not alter currents in non-NMDA receptors, suggesting that it is due to a selective action on NMDA receptors. As discussed above, peripheral NMDA receptors are expressed by nociceptors and their activation by MSG leads to reports of pain and sensitivity in

humans. Thus, it may be that arachidonic acid and MSG share a common mechanism for the induction of increased pain sensitivity.

Can dietary restriction of arachidonic acid alter chronic pain?

As humans cannot synthesize arachidonic acid de novo, it is feasible to reduce arachidonic acid levels through diets that restrict intake of linoleic acid, its precursor, and arachidonic acid [46]. Foods high in arachidonic acid include meats, dairy and eggs, so lowering of arachidonic acid intake may be accomplished by decreasing intake of these foods, e.g. a vegetarian diet.

A pre-clinical study done in rats tested the effect of reducing linoleic acid from 50% of to just 6.3% of the dietary intake of polyunsaturated fat on the development of signs of neuropathic pain produced by chronic constriction injury of the infraorbital nerve [57]. While the low linoleic acid diet slowed the development of mechanical sensitization, it did not prevent it from developing to a similar extent as animals who received a normal diet. Thus, by 2 weeks post induction of the nerve injury, both groups of rats had a similar decrease in mechanical threshold over the face. The low linoleic did, however, reduce plasma protein extravasation induced by capsaicin. As capsaicin induced plasma protein extravasation is due, in part, to the release of inflammatory mediators, this suggests that the diet may have lowered inflammatory response. Nevertheless, there was no long term benefit of the diet on the development of neuropathic-like pain in these animals.

Clinical trials in humans have been undertaken to examine the effectiveness of lowered arachidonic acid intake diets on arthritis and headache. In a study of rheumatoid arthritis patients, it was reported that reduction of dietary intake of arachidonic acid by $\frac{2}{3}$ of normal, lowered the number of painful joints by 14% [58]. A 20% reduction of pain after 3 months of the low arachidonic acid diet was also reported, however, it is debatable whether this modest effect on pain is clinically meaningful. These improvements in pain were associated with a decrease in the level of leukotriene B₄ in the blood [58]. As patients were allowed to remain on their drug therapy, which often included non-steroidal antiinflammatory drugs, there was little effect of the low arachidonic acid diet on prostaglandin E₂ levels.

In patients with headache, there have been more mixed results associated with low arachidonic acid diets. An earlier randomized, single-blinded, parallel-group study in chronic daily headache (mostly migraine) sufferers, compared a diet of low arachidonic acid intake (50% reduction) to a diet of that consisted of low arachidonic acid with increased consumption of omega 3 fatty acids [58,59]. It was found that reduction of dietary intake of arachidonic acid alone reduced headache days from an average of 23 to 19, and headache duration by 1 hour per headache. However, this study lacked a normal diet control group, so it is unclear how big the effect of simply being placed on a diet might have been, especially given the large placebo effect often seen in headache prophylaxis studies [59]. A more recent study using a similar low fat diet approach, failed to find any effect of the diet on the intensity, frequency or duration of migraine headaches [60]. At present, the effect of lowering arachidonic acid intake on migraine headache or rheumatoid arthritis pain appears modest, at best.

Caffeine and Pain

Caffeine is found in many foods and beverages consumed in the Western diet, most notably in coffee, with lesser amounts also found in soft drinks and chocolate. A cup of brewed coffee contains between 60 and 135 mg of caffeine [61]. In North America and Northern Europe, average daily consumption of caffeine ranges from 200-425 mg per day, with consumption in Scandinavia more than double consumption in the North America [61,62]. However, the current consensus is that intake of 200-400 mg of caffeine per day is not harmful to health and does not appear to increase pain complaints [61].

Association of caffeine with pain

Elevated daily consumption of caffeine (400–800 mg/day) is associated with increase anxiety, tachycardia, trembling and insomnia [63]. Some work suggests that consumption of more than 400 mg/day is a risk factor for the development of headaches [62,63]. Caffeine-related headaches are described as constant, dull, pressure like, and bilateral [61]. In a study of adult patients with chronic daily headache, it was reported that there appeared a higher daily consumption of caffeine prior to the onset of daily headaches, particularly in women with migraine headache [64]. However, daily caffeine intake was not predictive of headache in this study, and no cause-effect relationship between intake and headache could be established. In some children and adolescents who report daily headaches, caffeine consumption of over 200mg/day (in the form of soft drinks) appears to be the cause, as headaches resolve if caffeine intake is lowered [61].

Why does caffeine alter pain sensitivity?

Serum caffeine concentrations 1 hour after caffeine intake of 150 mg are around 10-30 μM [65]. Caffeine, in this concentration range, is a competitive antagonist at adenosine A_1 and A_{2A} receptors [63]. Antagonism of these receptors in the central nervous system by caffeine lengthens time to get to sleep (sleep latency), increases light over deep sleep and shortens total sleep time [63]. A polymorphism in the A_{2A} receptor that alters its sensitivity to caffeine may explain some of the individual differences in sleep sensitivity [63]. As sleep deprivation is associated with increased pain sensitivity and headaches, this may provide one reason why elevated daily intake of caffeine might be associated with headache pain. Another mechanism that may contribute to increased headaches is the ability of caffeine to reduce cerebral blood flow by competitive antagonism of the A_{2A} receptor [65]. In a study of low (~ 45 mg/day), moderate (~ 400 mg/day) and high (~ 900 mg/day) daily caffeine users, it was found that acute ingestion of caffeine reduced cerebral blood flow by about 20% [66]. High daily caffeine users had lower cerebral blood flow than moderate or low daily users [65].

Caffeine also promotes calcium influx that would also be expected to promote contraction of smooth muscle, although at high concentrations (5-30 mM) outside of the concentration range normally obtained through oral consumption of caffeine containing foods and beverages. However, recently it has been shown that 30 μM caffeine inhibits the action of the excitatory amino acid transporter type 3 (EAAT3) glutamate transporter [67]. Glutamate transporters remove glutamate from the extracellular space and, in the central nervous system, the EAAT3 is found mainly on neurons. Inhibition

of glutamate reuptake by a caffeine mediated block, could lead to elevated levels of glutamate. EAAT1-3 have been found to be expressed by trigeminal ganglion neurons and their associated satellite glial cells (Figure2) [68]. Indeed, inhibition of glutamate reuptake in the trigeminal ganglion leads to increased firing and mechanical sensitization of temporalis muscle nociceptors (Figure 3) [68]. As pain in the temporalis muscle is associated with headaches, the ability of caffeine to inhibit EAAT3 may also contribute to altered pain sensitivity and headache.

Does dietary restriction of Caffeine alter chronic pain?

It is recognized that abrupt cessation of caffeine intake in about half of regular consumers leads to a mild headache that is relieved by intake of caffeine [69-71]. Withdrawal headaches are associated with an increase in cerebral blood flow [65]. However, tapered withdrawal of caffeine over a period of 1-2 weeks (depending on daily intake), prevents the development of this headache. In children with caffeine associated headache, tapered withdrawal to no intake led to cessation of headache [61]. In a case report, reduction of caffeine intake from 360 mg/day to 2-10 mg/day resolved all pain symptoms in a 50 year old woman with trigeminal neuropathy, but no clinical study has ever been tried on this patient population [72]. In a single-blind, randomized clinical trial it was found that decreased consumption of caffeine did not decrease breast pain/tenderness in breast cancer sufferers [73]. Thus, at present, research suggests that caffeine withdrawal may be effective when caffeine is thought to be the cause of the pain condition, e.g. caffeine induced headache.

Conclusions:

The concept that certain food components or food additives cause acute pain symptoms is not new, but has not been subjected to rigorous scientific investigation in many cases. In some cases, such as MSG, a body of evidence does indicate that ingestion can lead to the development of specific pain complaints, however, it is not clear what the relationship of such findings are to the development and maintenance of chronic pain conditions. Thus, whether excessive intake of certain dietary components contributes to chronic pain conditions remains an open question. That being said, it is relatively easy to reduce consumption of caffeine, monosodium glutamate, aspartame and/or arachidonic acid in the diet, making this an attractive potential adjunctive treatment for certain patients with chronic pain conditions, in particular those with chronic headache or chronic musculoskeletal pain. Given the growing recognition that treating chronic pain conditions with long term pharmacotherapy is problematic, alternative therapies that include diet modification are likely to continue growing in popularity.

Reference Annotations: please highlight 6–8 references that are of particular significance to the subject under review as “* of interest” or “** of considerable interest” and provide a brief (1–2 line) synopsis.

*Schaumburg HH, Byck R, Gerstl R, Mashman JH. Monosodium L-glutamate: its pharmacology and role in the Chinese restaurant syndrome. *Science*, 163, 826-828 (1969).

This article contains one of the first descriptions of the effects of MSG, and was the catalyst for a series of research studies looking into the effects of MSG overconsumption.

*Shimada A, Baad-Hansen L, Castrillon E et al. Differential effects of repetitive oral administration of monosodium glutamate on interstitial glutamate concentration and muscle pain sensitivity. *Nutrition*, 31(2), 315-323 (2015).

This article describes the effect of daily intake of MSG on healthy young individuals, and shows for the first time in humans how glutamate levels in the masticatory muscle, a source of pain in temporomandibular disorders, are affected by consumption of MSG.

*Cairns BE, Dong X, Mann MK et al. Systemic administration of monosodium glutamate elevates intramuscular glutamate levels and sensitizes rat masseter muscle afferent fibers. *Pain*, 132(1-2), 33-41 (2007).

This is the first in vivo study demonstrating a relationship between glutamate concentrations and nociceptor sensitivity.

**Ferrari A, Spaccapelo L, Pinetti D, Tacchi R, Bertolini A. Effective prophylactic treatments of migraine lower plasma glutamate levels. *Cephalalgia*, 29(4), 423-429 (2009).

This study demonstrates that effective migraine prophylaxis is associated with a decrease in serum glutamate concentrations in migraineurs.

**Holton KF, Taren DL, Thomson CA, Bennett RM, Jones KD. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. *Clin Exp Rheumatol*, 30(6 Suppl 74), 10-17 (2012).

This very interesting study found that a subpopulation of fibromyalgia patients are MSG sensitive.

*Magnuson BA, Burdock GA, Doull J et al. Aspartame: a safety evaluation based on current use levels, regulations, and toxicological and epidemiological studies. *Crit Rev Toxicol*, 37(8), 629-727 (2007)

This article provides thorough review of the risks of aspartame intake.

*Wagner K, Vito S, Inceoglu B, Hammock BD. The role of long chain fatty acids and their epoxide metabolites in nociceptive signaling. Prostaglandins Other Lipid Mediat, 113-115, 2-12 (2014)

This comprehensive review examines the effects of polyunsaturated fatty acids on pain.

*Nehlig A. Effects of coffee/caffeine on brain health and disease: What should I tell my patients? Pract Neurol, (2015).

This is a useful reference for health care providers who are asked about caffeine intake by their patients.

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Figure Legends:

Figure 1. The line and scatter plots show the interstitial glutamate concentration in the masseter muscle measured by microdialysis before and after oral ingestion of 150 mg/kg of MSG or sodium chloride (arrows) by healthy human subjects. Subjects continued daily ingestion of MSG or sodium chloride (NaCl; 24 mg/kg) diluted with a 400 ml soda daily for 5 days. After 5 days, there was a significant increase in the peak interstitial concentration produced by ingestion of 150 mg/kg MSG. There was a significantly higher frequency of reports of nausea and headache after ingestion of MSG and NaCl. Adapted from [17].

Figure 2: The expression of excitatory amino acid transporter type 1 (EAAT1), EAAT2, and EAAT3 in the rat trigeminal ganglion is shown (green). Glutamine synthetase (GS) was used to identify satellite glial cells (red). EAAT1 & EAAT2 were expressed by satellite glial cells (arrows). EAAT2 was also expressed in some neurons. EAAT3 was predominantly expressed by neurons.

Figure 3. Microinjection of glutamate into the trigeminal ganglion results in action potential discharge and mechanical sensitization of muscle nociceptors in female rats (n=6 per group). The graph in A shows the median discharge evoked by repeated injection of glutamate (Glu), compared to when the NMDA receptor antagonist APV, or the EATT antagonist TFB-TBOA were added to the second injection of glutamate.

Repeated injection of glutamate resulted in relatively reproducible discharges that were attenuated by APV, and increased by TFB-TBOA. The graph in B shows the mechanical threshold of afferent endings before (B) and after the same treatments. Repeated injections of glutamate significantly reduced the median mechanical threshold. Addition of APV attenuated this mechanical sensitization. Addition of TFB-TBOA did not affect mechanical sensitization. Bars represent median cumulative discharge and lines indicate the interquartile range. *, $p < 0.05$.

Fig 1

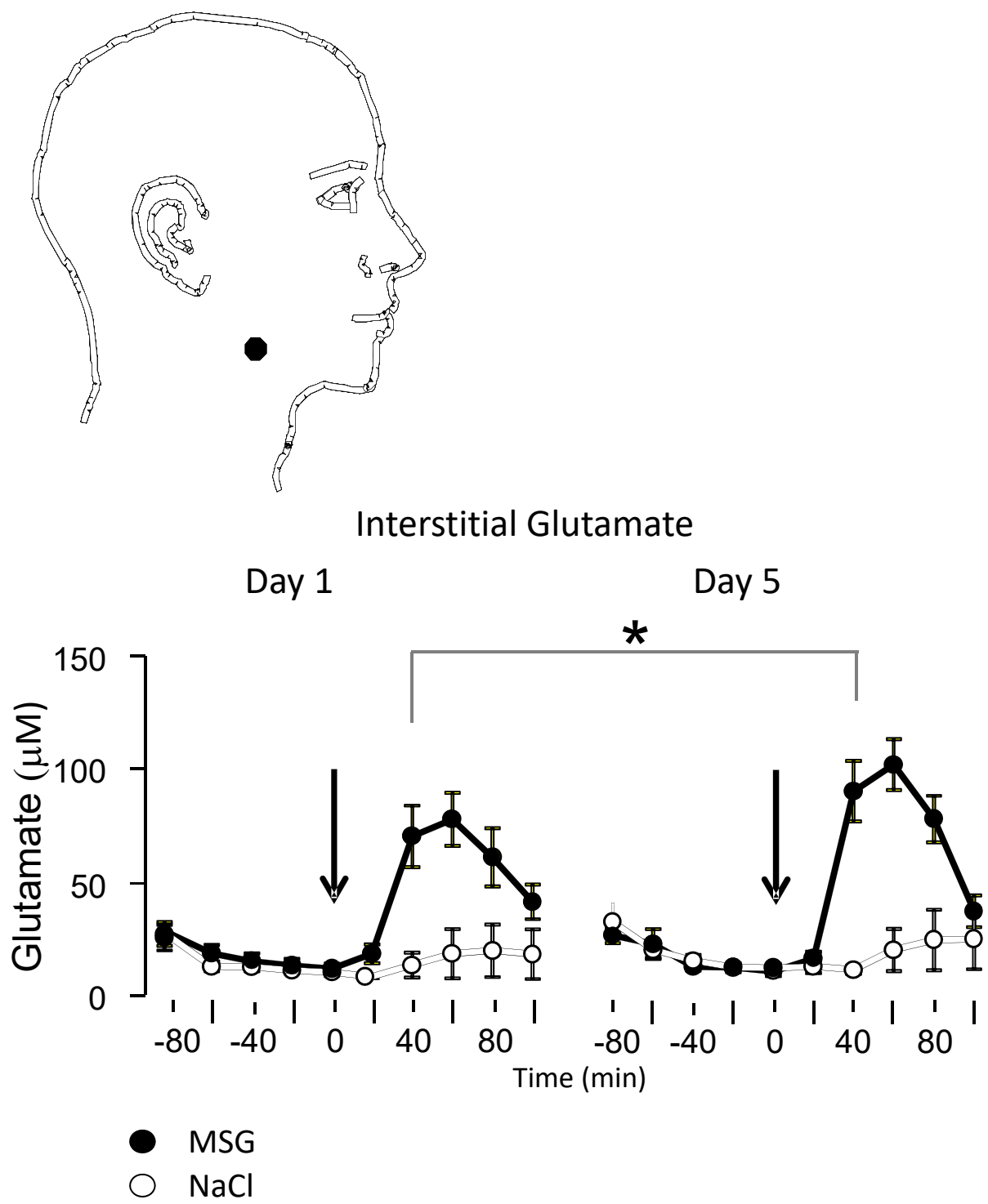
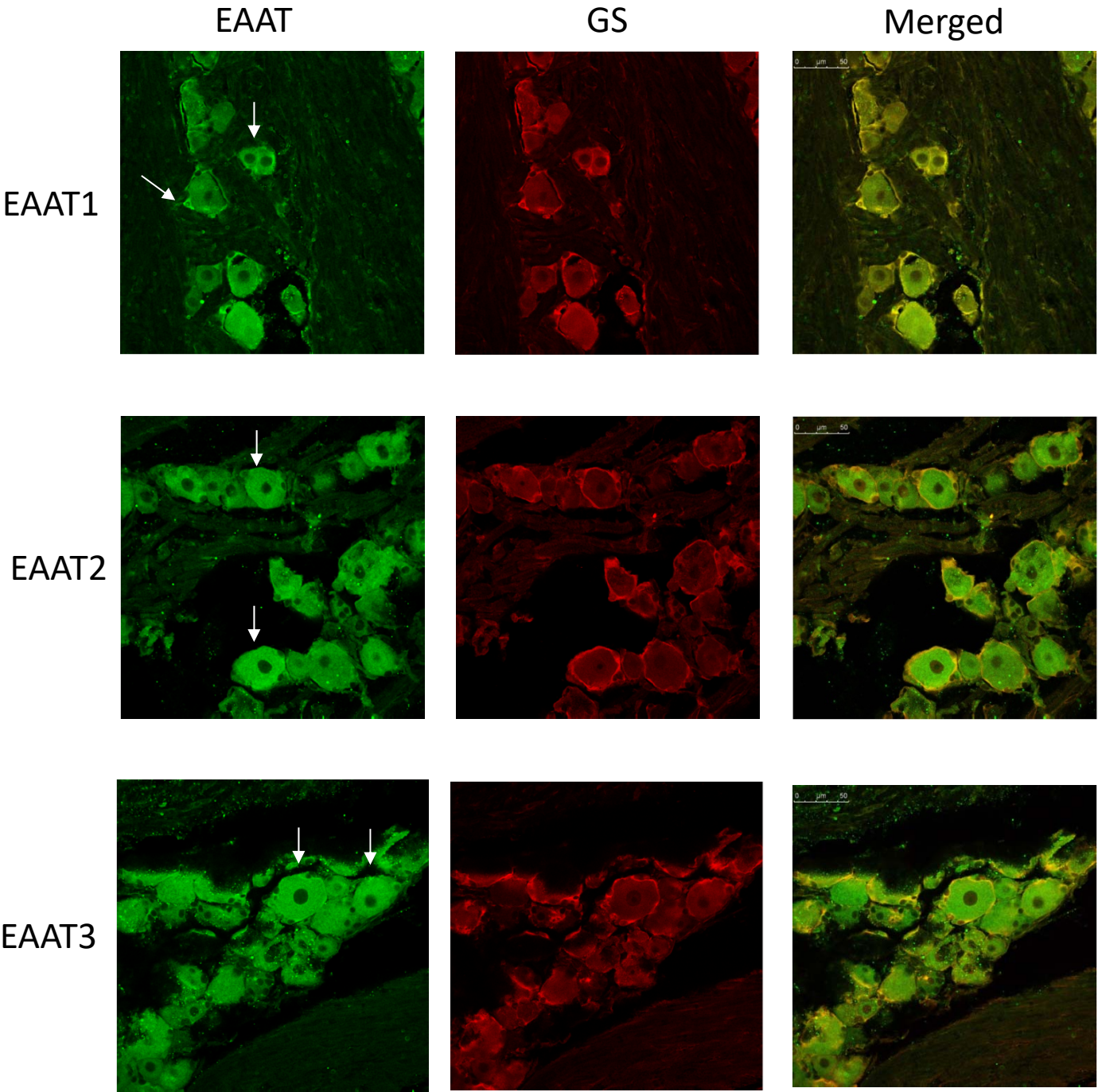


Fig 2



EAAT2

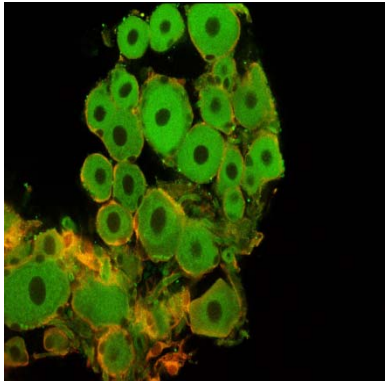
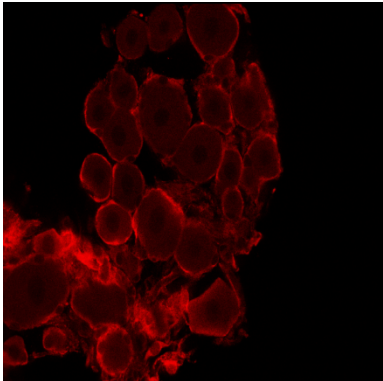
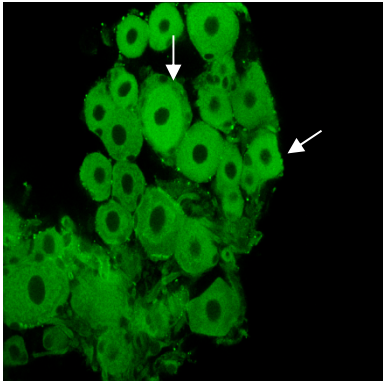
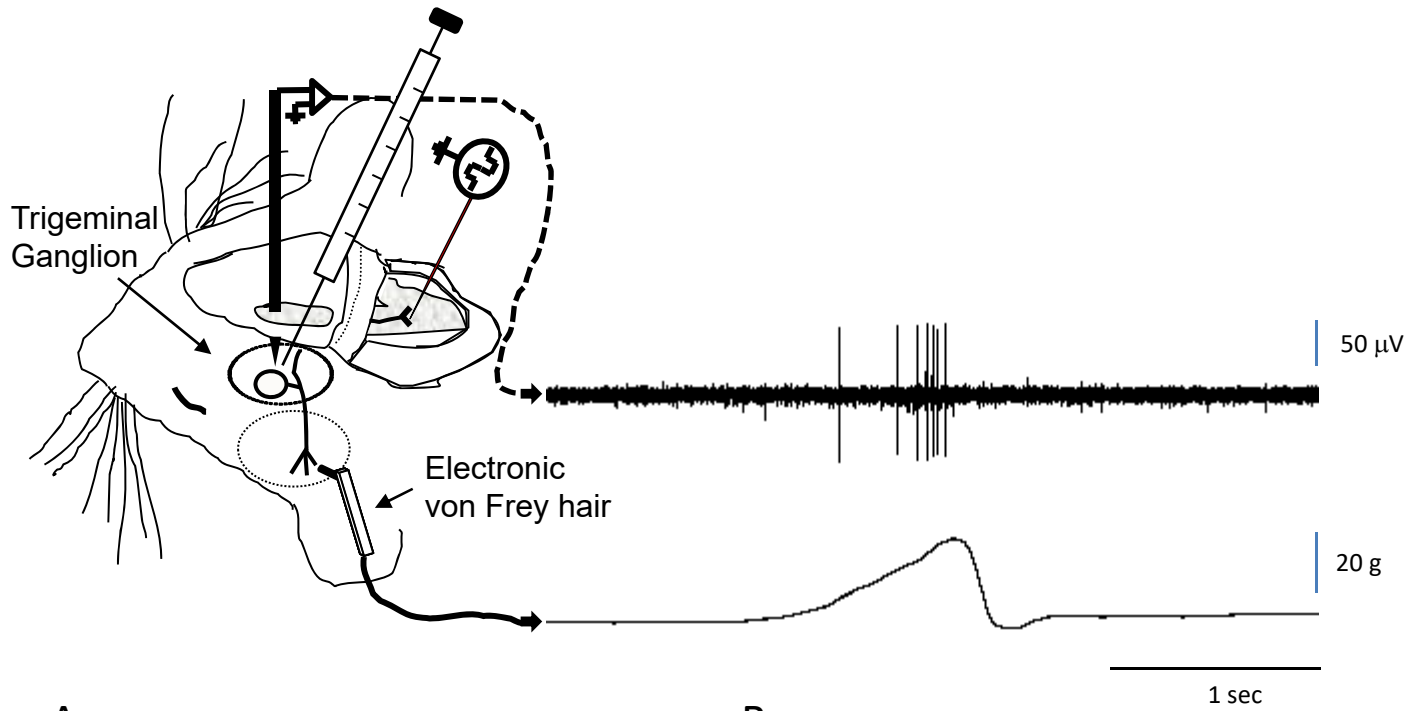
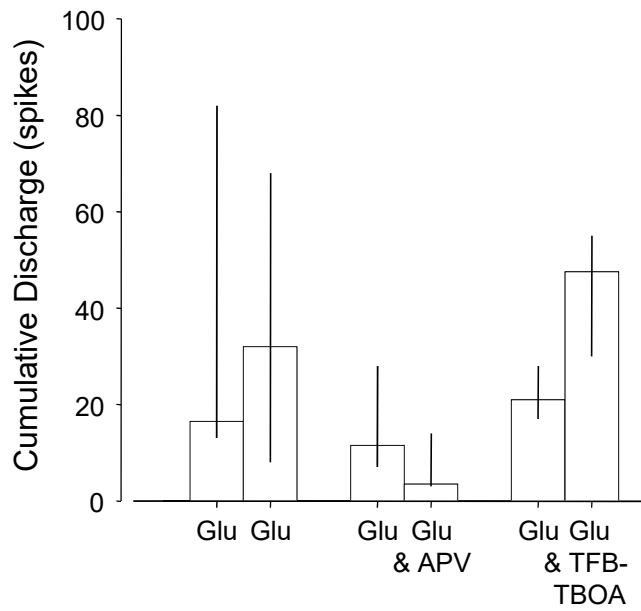


Fig 3



A



B

